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THE EFFECT OF PASSIVE HEAT STRESS AND EXERCISE-INDUCED DEHYDRATION ON THE COMPENSATORY RESERVE DURING SIMULATED HEMORRHAGE

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Abstract

Compensatory reserve represents the proportion of physiological responses engaged to compensate for reductions in central blood volume before the onset of decompensation. We hypothesized that compensatory reserve would be reduced by hyperthermia and exercise-induced dehydration, conditions often encountered on the battlefield. Twenty healthy males volunteered for two separate protocols during which they underwent lower-body negative pressure (LBNP) to hemodynamic decompensation (systolic blood pressure <80 mm Hg). During protocol #1, LBNP was performed following a passive increase in core temperature of ~1.2°C (HT) or a normothermic time-control period (NT). During protocol #2, LBNP was performed following exercise during which: fluid losses were replaced (hydrated), fluid intake was restricted and exercise ended at the same increase in core temperature as hydrated (isothermic dehydrated), or fluid intake was restricted and exercise duration was the same as hydrated (time-match dehydrated). Compensatory reserve was estimated with the compensatory reserve index (CRI), a machine-learning algorithm that extracts features from continuous photoplethysmograph signals. Prior to LBNP, CRI was reduced by passive heating [NT: 0.87 (SD 0.09) vs. HT: 0.42 (SD 0.19) units, P <0.01] and exercise-induced dehydration [hydrated: 0.67 (SD 0.19) vs. isothermic dehydrated: 0.52 (SD 0.21) vs. time-match dehydrated: 0.47 (SD 0.25) units; P <0.01 vs. hydrated]. During subsequent LBNP, CRI decreased further and its rate of change was similar between conditions. CRI values at decompensation did not differ between conditions. These

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results suggest that passive heating and exercise-induced dehydration limit the body's physiological reserve to compensate for further reductions in central blood volume.

Keywords

Compensatory reserve; dehydration; exercise; heat; hemorrhage

INTRODUCTION

Early detection and intervention are essential for the treatment of hemorrhage—the leading cause of death from trauma in civilian and military settings (1–4). On the battlefield, it is estimated that up to 25% of trauma deaths are potentially survivable with timely and effective intervention, with 85% of these deaths related to hemorrhage (3, 5). Therefore, tools and/or measures that can detect those in greatest need of immediate care have considerable implications for improving the survival of trauma victims.

Heart rate, arterial oxygen saturation, respiration, and blood pressure have long been standard vital signs used to assess the severity of an injury associated with trauma. However, relying upon these variables confounds the early detection of hemorrhage due to physiological compensatory mechanisms that maintain these vital signs to near normal values despite significant blood loss (6, 7). Such compensation may delay treatment until a state of cardiovascular decompensation is reached that culminates in profound hypotension, shock, and potentially death. The integration of all mechanisms that compensate for reductions in central blood volume has been termed compensatory reserve (8). To obtain an estimate of compensatory reserve, the compensatory reserve index was developed using extraction and machine-learning technology (7–10). Compensatory reserve index values are processed from features of the arterial waveform that provide an earlier and more specific marker of reductions in central blood volume compared with traditional vital signs (7, 11–14). For example, receiver operating characteristic (ROC) analysis showed that the compensatory reserve index detects low-volume blood loss following blood donation in human volunteers with greater specificity compared with systolic blood pressure, heart rate, cardiac output, and stroke volume (12). Furthermore, the compensatory reserve index can distinguish individuals with low vs. high tolerance to simulated hemorrhage (9) and tracks acute improvements in tolerance to simulated hemorrhage following intrathoracic pressure therapy (15). Importantly, the compensatory reserve index uses continuous peripheral pulsatile waveforms from a finger pulse oximeter, making it a practical measure in the prehospital setting.

Initial evaluation of the compensatory reserve index as a tool to monitor hemorrhage has necessarily used controlled blood draws or simulated hemorrhage. This study expands upon these controlled challenges to include physiological stressors encountered in a battlefield setting. Passive heat stress and exercise-induced dehydration are two conditions often encountered during military activities and in civilian settings (16–18). Both of these conditions reduce human tolerance to reductions in central blood volume (19, 20) and therefore represent ideal scenarios to test the ability of the compensatory reserve index to

track compensatory reserve during stressors encountered in the field. The primary purpose of this study was to test the hypothesis that compensatory reserve is reduced by passive heat stress and exercise-induced dehydration, prior to further reductions in central blood volume. A secondary purpose was to test the hypothesis that compensatory reserve decreases further during subsequent reductions in central blood volume and that these conditions do not affect the ability of the compensatory reserve index to predict impending decompensation.

PATIENTS AND METHODS

Subjects

A total of 20 male subjects, recruited from the Dallas/Fort Worth area, volunteered for two separate experimental protocols. For protocol #1, compensatory reserve was evaluated in 12 subjects, their mean (standard deviation) characteristics being: age, 32 (6) y [range: 22–41]; height, 182 (8) cm [range: 140–196]; mass, 83.5 (12.0) kg [range: 69.4–107.6]. For protocol #2, compensatory reserve was evaluated in eight subjects, their characteristics being: age, 35 (6) y [range: 27–44]; height, 184 (12) cm [range: 170–204]; mass, 85.1 (11.1) kg [range: 68.7–99.5]. All subjects were non-smokers, free of any known cardiovascular, respiratory, neurological, or metabolic diseases and not taking any related medications. For both protocols, trials were performed on separate days, at the same time of day within each subject and each trial was separated by a minimum of 8 weeks. Subjects were asked to refrain from strenuous physical activity for 24 h, as well as from caffeine and alcohol for 12 h prior to the experimental visits. The Institutional Review Boards at the University of Texas Southwestern Medical Center and at Texas Health Presbyterian Hospital Dallas approved all procedures and the consent form (STU 122011-011), the latter of which was obtained from all subjects prior to their participation. All studies were performed at the Institute for Exercise and Environmental Medicine in Dallas, TX.

Experimental overview

Compensatory reserve was examined during simulated hemorrhage following whole-body passive heat stress (protocol #1) and exercise in the heat (protocol #2). For protocol #1, a subset of the data investigating tissue oxygen saturation during simulated hemorrhage has been published (21), while a subset of the data investigating the effects of dehydration on tolerance to simulated hemorrhage has been published for protocol #2 (19). Herein, measurements of compensatory reserve obtained as part of these experimental protocols are presented. For both protocols, compensatory reserve was evaluated using the compensatory reserve index during progressive lower body negative pressure (LBNP) to hemodynamic decompensation, a validated model of simulated hemorrhage in humans (22, 23).

Measurements common to both protocols

Core temperature was measured with a telemetric pill (HQ Inc, Palmetto, FL) that was swallowed a minimum of 60 min prior to data collection. Mean skin temperature was measured as the weighted average of six thermocouples attached to the skin surface on the abdomen (14%), calf (11%), chest (22%), lower back (19%), thigh (13%), and upper back (21%). Body mass measurements were obtained with a scale (Health o meter Professional Scales, McCook, IL) accurate to 0.1 kg. Changes in body mass during the protocols were

corrected for fluid intake and urine loss. Heart rate was obtained from an electrocardiogram (GE Healthcare, Milwaukee, WI). Continuous blood pressure measurements were obtained noninvasively using photoplethysmography (Finometer Pro, FMS, Amsterdam, The Netherlands). Continuous photoplethysmograph waveforms were recorded from a finger pulse oximeter (Nonin Medical Inc, Plymouth, MN). The CipherOx CRI system (V2.0.1, Flashback Technologies Inc, Boulder, CO) was used to estimate compensatory reserve index values from the recorded photoplethysmograph signals. This novel approach exploits properties of the continuous pulsatile waveforms to estimate the patient's remaining reserve to cardiovascular decompensation. Compensatory reserve index values range between 0 and 1, where 0 represents imminent cardiovascular instability/decompensation and 1 represents maximal capacity for physiological mechanisms to compensate for reductions in central blood volume (7, 9, 10).

Experimental protocol #1

Subjects visited the laboratory on two occasions. Upon arrival, subjects swallowed the telemetric pill before providing a urine sample and weighing themselves nude. Dressed in shorts, subjects were then instrumented for the measurement of heart rate, blood pressure, and mean skin temperature before donning a two-piece tube-lined suit (Med-Eng, Ottawa, ON, Canada) that covered the entire body except for the head, hands, feet, and one forearm. While supine, the subjects were sealed at the waist within a custom made LBNP chamber. A pulse oximeter was placed on one of the subjects' fingers and water maintained at 34°C was circulated through the suit for a baseline period that lasted a minimum of 45 min. After baseline data collection, the subjects underwent either whole-body passive heat stress ("hyperthermic" condition, HT) or remained normothermic for a time-control period ("normothermic" condition, NT). All subjects performed both conditions, the order of which was randomized: five subjects performed the NT trial first, seven performed the HT trial first. Whole-body passive heat stress was achieved by circulating 49°C water through the suit until core temperature increased by ~1.2°C, whereas water temperature remained at 34°C during the time-control period which lasted 40 to 60 min. Upon achieving the desired increase in core temperature, or following the time-control period, incremental LBNP to hemodynamic decompensation was performed. The LBNP protocol began at 20 mm Hg, with a 10 mm Hg increase in LBNP every 3 min until decompensation. Criteria for determining decompensation included: continued self-reporting by the subject of feeling faint, sustained nausea, rapid and progressive decrease in blood pressure resulting in a sustained systolic blood pressure <80 mm Hg, and/or relative bradycardia accompanied by a narrowing of pulse pressure.

Experimental protocol #2

Subjects visited the laboratory on four occasions. The first visit consisted of a preliminary session to determine maximum oxygen uptake (VO_2max) using a protocol previously described for our laboratory (24). The remaining visits consisted of the experimental trials. Upon arrival, subjects swallowed the telemetric pill before providing a urine sample and weighing themselves nude. Dressed in shorts and running shoes, subjects were instrumented for the measurement of heart rate, blood pressure, and mean skin temperature before lying in the supine position for a baseline period that lasted a minimum of 30 min at a room

temperature of ~24°C. A baseline blood sample was drawn at the end of the baseline period and subjects were subsequently transferred to a climate controlled chamber regulated at a temperature of 41°C and a relative humidity of 25%. Approximately 10 min after entering the chamber, subjects began treadmill exercise with the speed and inclination adjusted to elicit a metabolic heat production equivalent to sustained moderate to heavy military activities (~545 W), such as a dismounted foot patrol (25). Oxygen consumption during exercise averaged ~1.8 L/min [~45% of VO_2max: 4.04 (1.07) L/min, range: 2.59–6.20] whereas metabolic heat production averaged ~540W across the three conditions. To promote sweat evaporation, a fan was placed in front of the subjects that provided an air velocity of ~5 m/s. Every 15 min during exercise, changes in body mass were measured upon subjects momentarily stepping off the treadmill and drying the skin surface with a towel. Baseline and end-exercise blood pressure measurements were obtained by automated auscultation of the brachial artery (Tango+; SunTech Medical, Morrisville, NC).

The three experimental visits differed in the level of dehydration that was achieved during exercise. During the first visit, subjects exercised for 90 min and fluid loss was replaced by having subjects drink warm (38°C) water administered in aliquots based upon the body mass measurements taken every 15 min (“hydrated” condition). During the second visit, subjects did not consume any fluid and exercise continued until core temperature increased to the same level as that observed during the hydrated condition (“isothermic dehydrated” condition). During the third visit, subjects did not consume any fluid and exercised for 90 min (“time-match dehydrated” condition). Immediately after exercise, subjects remained in the chamber maintained at 41°C and 25% relative humidity and were positioned within a custom-made LBNP chamber. A pulse oximeter was placed on the subject’s finger to measure compensatory reserve. Once the transition from the treadmill to the LBNP chamber was complete, a blood sample was drawn following which incremental LBNP to decompensation was performed as described for protocol #1. A final blood sample was drawn immediately after the termination of the LBNP protocol. The venous blood samples were subsequently analyzed for hemoglobin, hematocrit (both via fluorescent flow cytometry), and plasma osmolality (via osmometry). The study was originally designed to compare the dehydrated and isothermic dehydrated conditions. All subjects therefore performed the dehydrated trial first to determine the target increase in core temperature for the isothermic dehydrated trial. However, this approach resulted in a substantially shorter exercise duration during the isothermic dehydrated trial (see the Results section). The time-match dehydrated trial was added *post-hoc* to account for differences in exercise time. The order in which the conditions were performed was therefore not randomized.

Data analysis

Data were collected with data acquisition hardware and software (Biopac Systems Inc, Santa Barbara, CA) at a minimum sampling frequency of 50 Hz. Data were analyzed as a one-group, within-subjects repeated measures design. A 1-min average of the data at each LBNP level was used for analyses. Tolerance to simulated hemorrhage was quantified using the cumulative stress index, calculated by summing the product of LBNP level and the time at each level (e.g. 20 mm Hg × 3 min + 30 mm Hg × 3 min + 40 mm Hg × 1 min = 190 mm Hg × min). For protocol #2, relative changes from baseline in plasma volume were calculated

from hemoglobin and hematocrit values (26). Investigators were not blinded to the conditions when performing data analyses.

Statistical analyses

Within each experimental protocol, dependent variables were analyzed using generalized estimating equations (GEE) with compound symmetry covariance structures for longitudinal correlated data analysis of continuous variables (compensatory reserve index, heart rate, and mean arterial pressure) and the dichotomous outcome of decompensation with the repeated factors of LBNP level for each experimental condition (27–29). ROC analysis was conducted by performing GEE repeated measures logistic regression on the dichotomous outcome of decompensation, which was measured at each increment of LBNP (14, 27, 30). The ROC area under the curve (ROC AUC) with 95% confidence intervals was calculated to assess the ability of the compensatory reserve index to predict decompensation under each experimental condition. Within each protocol, tolerance to simulated hemorrhage was analyzed using a Kaplan–Meier curve by plotting the cumulative stress index that was tolerated by each subject. The Kaplan–Meier curves were statistically compared between conditions with a log-rank Mantel–Cox test. For all analyses, the level of significance was set at an alpha of $P \leq 0.05$, with the exception of GEE analysis of longitudinal data across each LBNP level, for which P values were adjusted for multiple comparisons by dividing 0.05 by the number of tests resulting in alpha being set at $P \leq 0.005$ for the normothermic condition, $P \leq 0.007$ for the hyperthermic condition, $P \leq 0.006$ for the hydrated condition, $P \leq 0.007$ for the isothermic dehydration condition, and $P \leq 0.008$ for the time-match dehydration condition. Descriptive statistical analyses were performed using commercially available statistical software (Prism 6, Graphpad Software Inc, La Jolla, CA). GEE procedures for longitudinal correlated data were performed using SAS, version 9.4 (Cary, NC). All variables are reported as mean (standard deviation) unless otherwise indicated.

RESULTS

Experimental protocol #1

Baseline measures were similar between conditions (all $P > 0.10$, Table 1). Whole-body passive heat stress increased mean skin and core temperatures as well as heart rate, whereas it decreased mean arterial pressure and compensatory reserve index relative to the normothermic time-control period (all $P \leq 0.03$). Tolerance to simulated hemorrhage was reduced by heat stress [NT: 920 (718) vs. HT: 254 (177) mm Hg × min, $P < 0.01$], such that the tolerance curve was significantly shifted to the left by heat stress ($P < 0.01$, Fig. 1). Mean arterial pressure did not consistently change during progressive LBNP under the normothermic condition, but did so under the hyperthermic condition (Fig. 2). In contrast, progressive LBNP to decompensation resulted in consistent, time-dependent increases in heart rate under both conditions (Fig. 2). At the point of decompensation (Table 1), heart rate was greater during the hyperthermic condition ($P < 0.01$) whereas mean arterial pressure was similar between conditions ($P = 0.94$). The compensatory reserve index decreased across levels of LBNP during both conditions, although values were lower during the hyperthermic condition (Fig. 3). However, compensatory reserve index was similar between conditions at decompensation [NT: 0.18 (0.16) vs. HT: 0.13 (0.08), $P = 0.33$). Analysis of ROC curves

(Fig. 4) and ROC AUC values during normothermic (0.90, 95% CI: 0.82–0.99) and hyperthermic (ROC AUC: 0.78, 95% CI: 0.66–0.90) conditions demonstrate the ability of the compensatory reserve index to predict impending decompensation regardless of thermal status. Although the mean ROC AUC values during the hyperthermic condition were lower relative to the normothermic condition, they were not statistically different between conditions due to the overlapping confidence intervals. The change in CRI as a function of absolute LBNP time did not differ between NT [−0.042 (0.010) units/min] and HT [−0.049 (0.042) units/min, $P = 0.52$]. Individual compensatory reserve index tracings for each condition are presented in Figure 5.

Experimental protocol #2

Baseline measures were similar between conditions (all $P > 0.10$, Table 2). During exercise in the hydrated condition, all subjects exercised for 90 min and fluid replacement maintained body mass ($P = 0.69$, Table 2). Relative to the hydrated condition, exercise duration was shorter and reductions in body mass greater during the isothermic dehydrated condition (both $P \leq 0.01$, Table 2). By design, end-exercise core temperature did not differ between conditions ($P = 0.90$). During the time-match dehydrated condition, all subjects exercised for 90 min. Relative to the hydrated and isothermic dehydrated conditions, body mass loss and core temperature were greater at the end of exercise for the time-match dehydrated trial (both $P \leq 0.01$, Table 2). Following exercise, plasma osmolality was different between conditions ($P \leq 0.01$), being greater during the isothermic and time-match dehydrated conditions relative to hydrated (Table 2). In contrast, changes in plasma volume were not statistically different between conditions ($P = 0.07$, Table 2).

The transition from end-exercise to the start of LBNP averaged 19 (3) min and did not differ between conditions ($P = 0.67$). Prior to LBNP, no differences in mean arterial pressure were observed between conditions (Table 2). In contrast, heart rate was greater during the time-match dehydrated condition relative to the hydrated condition ($P \leq 0.01$, Table 2). Furthermore, compensatory reserve index was lower in both dehydrated conditions relative to the hydrated condition (both $P \leq 0.01$). Tolerance to simulated hemorrhage was reduced by dehydration, although differences did not reach statistical significance [hydrated: 532 (193) vs. isothermic dehydrated: 430 (197) vs. time-match dehydrated: 331 (85) mmHg × min, $P = 0.08$]. Nonetheless, the Kaplan–Meier curves were statistically different when comparing all three conditions ($P = 0.04$, Fig. 1). When analyzed separately, a statistical difference was only observed between the hydrated and time-match dehydrated conditions ($P < 0.01$). The tolerance curves for hydrated versus isothermic dehydrated ($P = 0.42$) and isothermic dehydrated versus time-match dehydrated ($P = 0.18$) were not statistically different.

During progressive LBNP, mean arterial pressure remained relatively unchanged until the later stages of LBNP (Fig. 6). In contrast, consistent increases in heart rate (Fig. 6) and decreases in compensatory reserve index (Fig. 3) were observed under all conditions. At decompensation, mean arterial pressure and heart rate (Table 2) as well as compensatory reserve index were similar between conditions [hydrated: 0.10 (0.06) vs. isothermic: 0.11 (0.06) vs. time-match: 0.10 (0.07), $P = 0.98$). Analysis of ROC curves (Fig. 4) and ROC AUC values during hydrated (0.93, 95% CI: 0.84–0.99), isothermic dehydrated (0.81, 95%

CI: 0.65–0.97), and time-match dehydrated (0.85, 95% CI: 0.68–0.99) conditions demonstrate the ability of the compensatory reserve index to predict impending decompensation regardless of hydration status. Although the mean ROC AUC values during both dehydrated conditions were lower relative to the hydrated condition, these differences were not statistically different due to the overlapping confidence intervals. The change in compensatory reserve index as a function of absolute LBNP time did not differ between conditions [hydrated: −0.043 (0.019) vs. isothermic dehydrated: −0.036 (0.021) vs. time-match dehydrated: −0.038 (0.027) units/min, $P = 0.43$]. Individual compensatory reserve index tracings are presented in Figure 7.

DISCUSSION

The current study examined whether the compensatory reserve index tracks reductions in tolerance to simulated hemorrhage during stressors encountered on the battlefield. The main findings show that passive heat stress and exercise-induced dehydration reduced compensatory reserve prior to the onset of simulated hemorrhage. Furthermore, compensatory reserve index values decreased progressively during simulated hemorrhage and were a strong predictor of impending hemodynamic decompensation based on ROC analysis. These data suggest that the compensatory reserve index appropriately tracks reductions in the physiological reserve to compensate for simulated hemorrhage during whole-body passive heat stress and following exercise-induced dehydration.

The compensatory reserve index has recently been introduced as an innovative clinical tool to continuously and noninvasively monitor the physiological reserve to tolerate central blood volume loss (7–10). Importantly, the compensatory reserve index provides an earlier and more specific indicator of such changes compared with traditional vital signs (9, 11–13). Furthermore, it can be incorporated into standard monitors that generate an arterial waveform, such as a finger pulse oximeter, making it an easy measure to integrate in the prehospital setting. Prior to the current study, however, it remained unknown if the compensatory reserve index appropriately tracks reductions in the physiological reserve to compensate for central blood volume loss during conditions often encountered by individuals at relatively greater risk of hemorrhagic injury (16–18), such as military personnel, firefighters, miners, etc. We therefore examined the effect of two conditions that reduce tolerance to simulated hemorrhage and that are often encountered in a field setting; whole-body passive heat stress and exercise-induced dehydration (19, 20). Both conditions reduced compensatory reserve prior to the onset of simulated hemorrhage (Fig. 3). A reduction in compensatory reserve implies that individuals are closer to the point of hemodynamic decompensation. In other words, a lower compensatory reserve index value indicates that less compensatory reserve is available to tolerate further reductions in central blood volume. The lower compensatory reserve index values prior to simulated hemorrhage during passive heat stress and following exercise-induced dehydration suggest that these conditions already engage physiological responses to compensate for the reduction in central blood volume they elicit (31, 32). It is important to note that, on average, compensatory reserve further decreased with subsequent simulated hemorrhage during both conditions. Our observation that compensatory reserve index values at the time of hemodynamic decompensation were similar regardless of condition supports the notion that the onset of

hemodynamic decompensation is dictated by the depletion of compensatory reserve. Furthermore, the change in compensatory reserve index as a function of absolute LBNP time was not affected by the experimental conditions tested. Overall, these results suggest that maximal physiological responses to compensate for central blood volume loss are finite, and that reduced tolerance to simulated hemorrhage following passive heat stress and exercise-induced dehydration are due to less reserve available for physiological responses to compensate for further central blood volume loss.

Results from ROC analyses indicate that the compensatory reserve index is a good predictor of impending hemodynamic decompensation, regardless of thermal or hydration status (Fig. 4). Importantly, ROC AUC values during the hyperthermic and dehydrated conditions were not significantly different from those observed during the normothermic and hydrated conditions. These findings suggest that passive heat stress and exercise-induced dehydration do not affect the ability of the compensatory reserve index to predict impending hemodynamic decompensation during simulated hemorrhage. Prior to simulated hemorrhage, compensatory reserve index decreased in every subject during whole-body passive heat stress (Fig. 5). Furthermore, most subjects (10/12) displayed a further reduction in compensatory reserve index during simulated hemorrhage while heat stressed. The lack of further change in compensatory reserve index in 2 of the subjects (#10 and 11) could be related to these subjects having engaged all of their physiological reserve prior to simulated hemorrhage to compensate for the cardiovascular adjustments associated with heat stress. This reinforces the notion that passive heat stress reduces the reserve for physiological compensation during further reductions in central blood volume, therefore resulting in dramatically reduced tolerance time (Fig. 1). In contrast, not all subjects displayed a reduced compensatory reserve index following exercise-induced dehydration (Fig. 7). Interestingly, when compensatory reserve index was not affected by dehydration (isothermic or time-match), tolerance time to simulated hemorrhage was similar to that observed during the hydrated condition (e.g. subjects #2, 4, 8 of Fig. 7). These results highlight interindividual variability in compensatory responses to reductions in central blood volume that were recognized by the compensatory reserve index.

The mechanisms by which heat stress, with or without dehydration, reduces tolerance to simulated hemorrhage are multifactorial (33). The reduction in compensatory reserve with passive heating and exercise-induced dehydration demonstrates the ability of the compensatory reserve index to capture physiological changes that occur with these conditions. The precise factor(s) responsible for reduced compensatory reserve cannot be identified because of individual variations in the integration of physiological mechanisms that compensate for central blood volume loss (34). However, it follows that passive heat stress and exercise-induced dehydration must affect properties of the photoplethysmograph waveforms from which compensatory reserve index is derived (7, 9, 10).

Perspectives

The current results suggest that measurements of compensatory reserve appropriately track reductions in tolerance to simulated hemorrhage following whole-body passive heat stress and exercise-induced dehydration. Previous studies established the compensatory reserve

index as an early and specific indicator of reductions in central blood volume under well-controlled environmental and physiological conditions (i.e., at rest, normothermic and hydrated). The current findings therefore extend previous studies to conditions often encountered in the field by individuals who are at relatively greater risk of hemorrhagic injury. The present findings are important if the compensatory reserve index is to be used as a clinical triage tool in the prehospital setting. Furthermore, compensatory reserve index values were obtained from photoplethysmograph signals making the results applicable to a field setting, where enhanced finger pulse oximeters—which are part of first responder medical kits—could be used to obtain compensatory reserve index measurements.

Considerations

It should be considered that hemorrhage was simulated in the current study with the use of progressive LBNP to hemodynamic decompensation. Although this represents a valid model of hemorrhage in humans under normothermic/hydrated conditions (22, 23), it remains unknown if progressive LBNP is an equally valid model of hemorrhage in heat-stressed/dehydrated humans. It should also be considered that the current results are specific to the population (young healthy males) and conditions employed. Analyses were executed within a one-group, within-subject experimental design. The relatively small size and potential for increased variability of compensatory reserve index values due to the physiological stressors examined may have led to underestimates of the true predictive ability of the compensatory reserve index (as measured by ROC AUC). It therefore remains to be determined if the compensatory reserve index adequately tracks changes in the physiological capacity to tolerate central blood volume loss in larger populations inclusive of other demographic groups (females, the elderly, etc.), as well as during other conditions often encountered in a field setting (e.g. altitude/hypoxia, cold stress, energy deprivation, nicotine/caffeine use, etc.). Finally, the current results suggest that the compensatory reserve index adequately tracks reductions in tolerance to simulated hemorrhage following passive heat stress and exercise-induced dehydration. It therefore remains to be determined if countermeasures that improve tolerance to simulated hemorrhage under these conditions (e.g. volume loading, skin-surface cooling, etc.) are paralleled by an improvement in compensatory reserve.

CONCLUSION

In conclusion, we examined the effect of passive heat stress and exercise-induced dehydration on the physiological reserve to compensate for reduced central blood volume, as estimated by the compensatory reserve index. The results show that passive heat stress and exercise-induced dehydration reduce compensatory reserve. However, these conditions do not affect the ability of the compensatory reserve to predict impending hemodynamic decompensation during subsequent simulated hemorrhage. These observations suggest that reduced tolerance to simulated hemorrhage under these conditions is due to less initial reserve to compensate for further central blood volume loss. The results also suggest that the compensatory reserve index appropriately tracks reductions in tolerance to simulated hemorrhage during conditions often encountered in the field by individuals at relatively greater risk of hemorrhagic injury.

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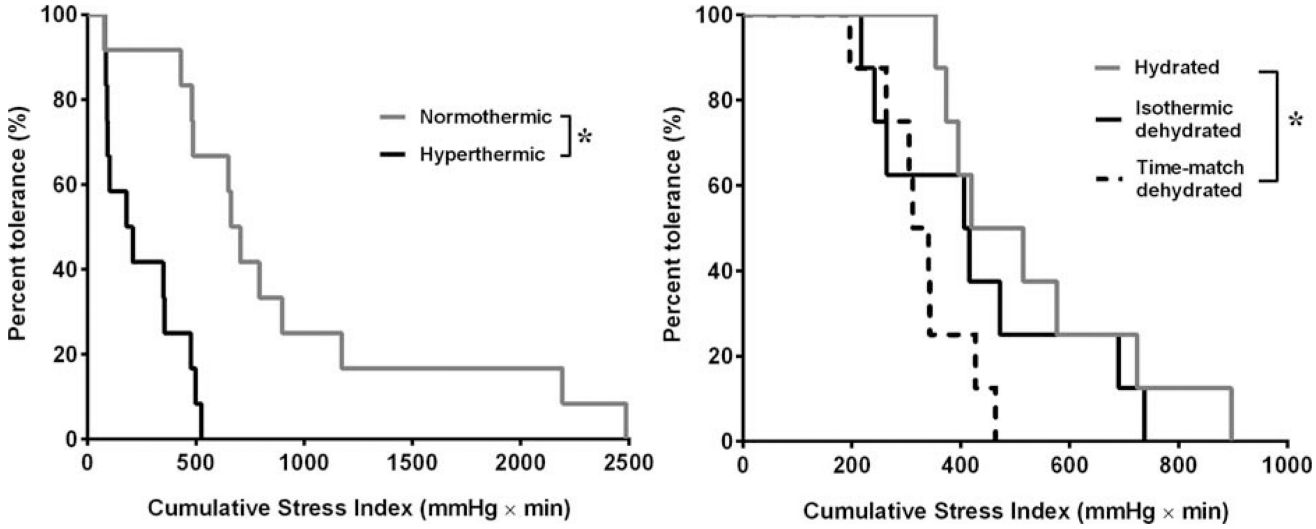

Fig. 1. Kaplan–Meier curves plotting the percent of individuals who tolerated a given cumulative stress index during simulated hemorrhage

The left panel presents data during the hyperthermic and normothermic conditions of protocol #1. The right panel presents data during the hydrated, isothermic dehydrated, and time-match dehydrated conditions of protocol #2. Significant ($P \leq 0.05$) difference between the normothermic and hyperthermic curves (left panel) and between the hydrated and time-match dehydrated curves (right panel) based on Log-Rank (Mantel–Cox) test.

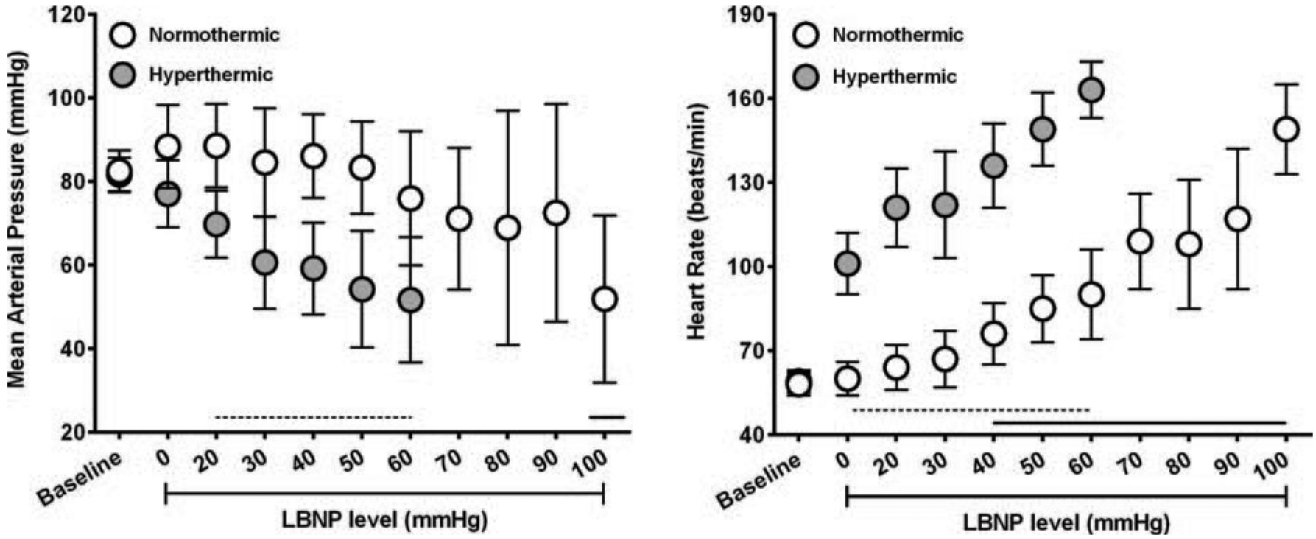

Fig. 2. Mean arterial pressure (left panel) and heart rate (right panel) during progressive lower body negative pressure (LBNP) to hemodynamic decompensation performed following whole-body passive heat stress (hyperthermic) or a normothermic time-control period (protocol #1)

The data are presented as mean ± 95% confidence intervals and were modeled using generalized estimating equations to account for differences in LBNP level at decompensation. Solid line, significantly different from baseline for normothermic. Dashed line, significantly different from baseline for hyperthermic.

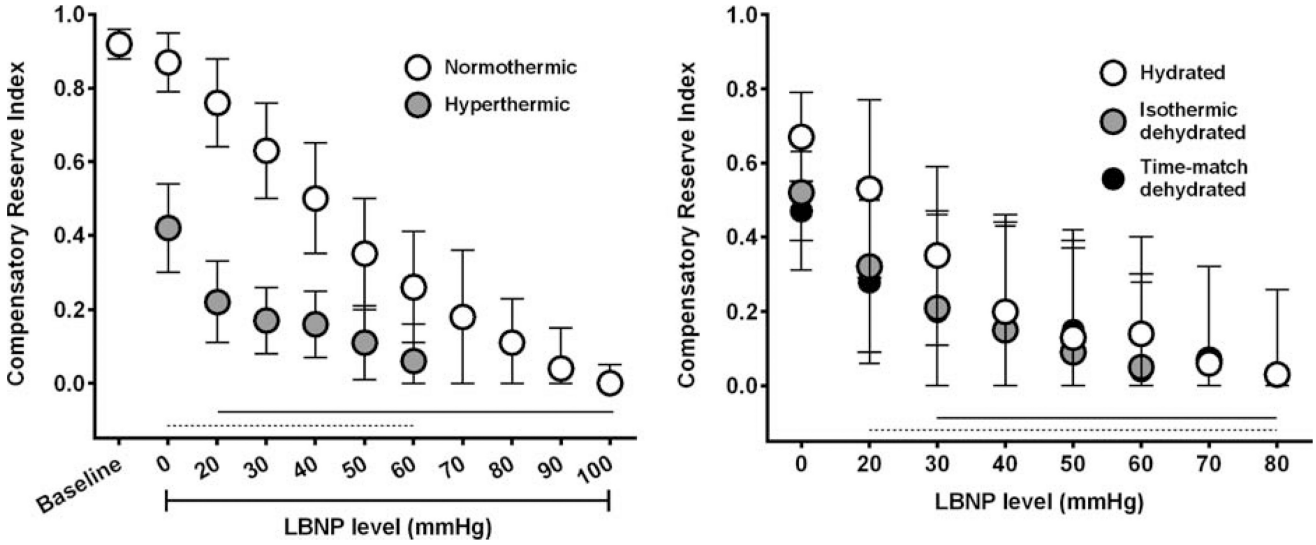

Fig. 3. The compensatory reserve index during progressive lower body negative pressure (LBNP) to hemodynamic decompensation

The left panel presents data during the hyperthermic and normothermic conditions of protocol #1. The right panel presents data during the hydrated, isothermic dehydrated, and time-match dehydrated conditions of protocol #2. The data are presented as mean ± 95% confidence intervals and were modeled using generalized estimating equations to account for differences in LBNP level at decompensation. Solid line, significantly different from baseline for normothermic and hydrated. Dashed line, significantly different from baseline for hyperthermic and isothermic/time-match dehydrated.

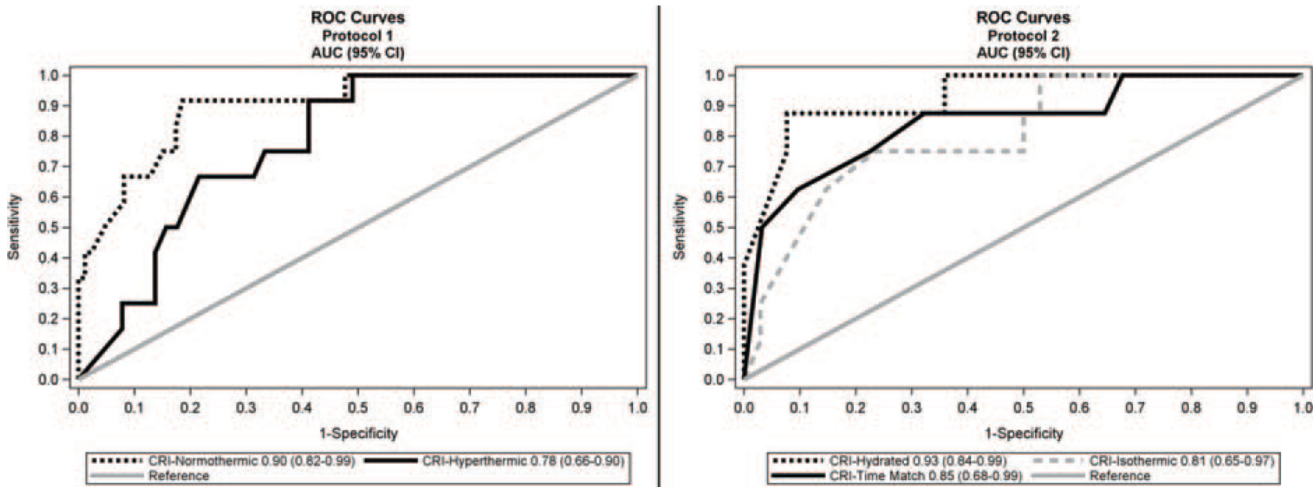

Fig. 4. Receiver operating characteristic (ROC) curves with area under the curve (AUC) values and 95% confidence intervals for the compensatory reserve index during the normothermic and hyperthermic conditions of protocol #1 (left panel); and during the hydrated, isothermic dehydrated and time-match dehydrated conditions of protocol #2 (right panel)

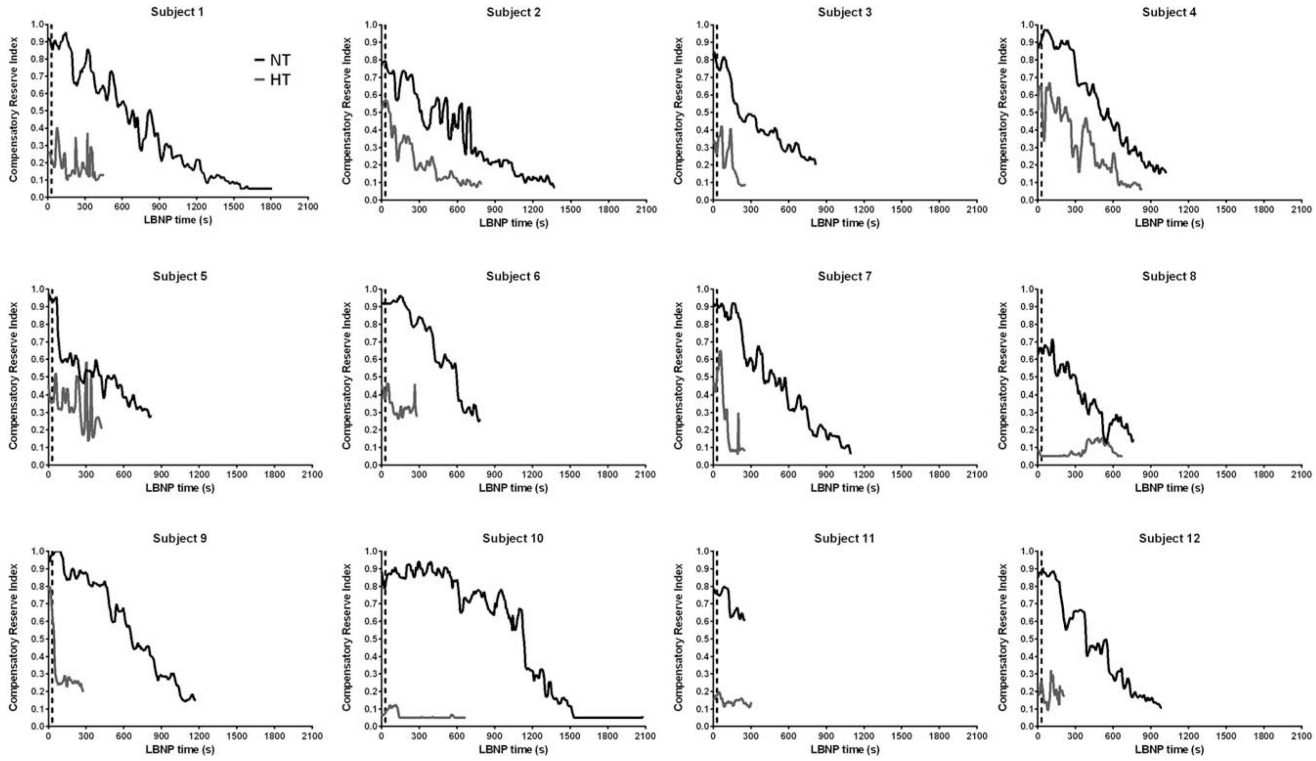

Fig. 5. Individual compensatory reserve index tracings during progressive lower body negative pressure (LBNP) to hemodynamic decompensation performed following whole-body passive heat stress (HT) and a normothermic (NT) time-control period (protocol #1)

The dashed line indicates the start of LBNP.

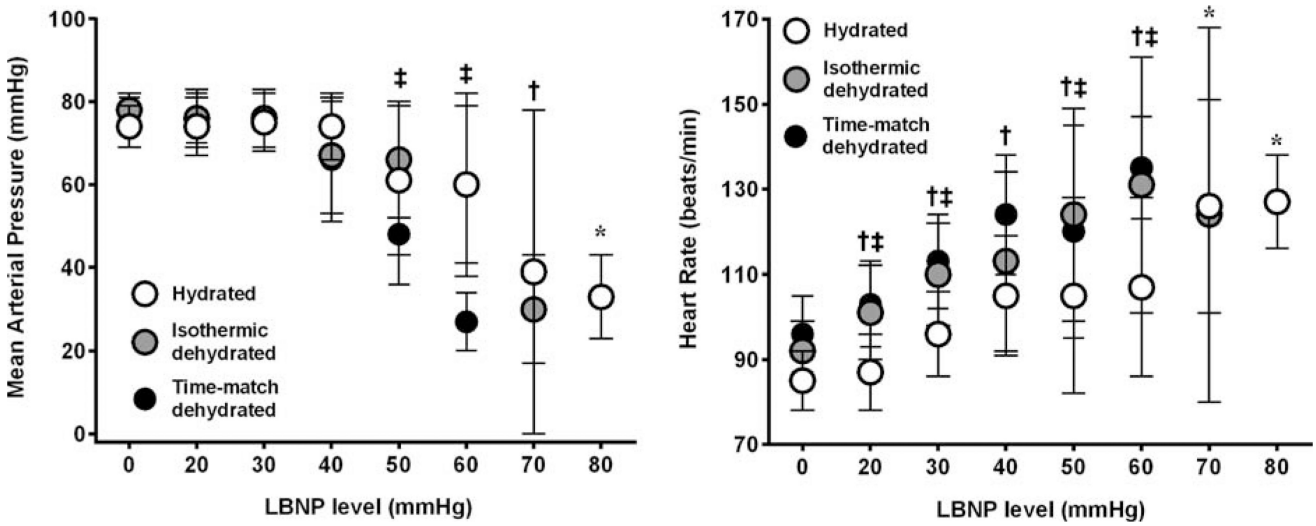

Fig. 6. Mean arterial pressure (left panel) and heart rate (right panel) during progressive lower body negative pressure (LBNP) to hemodynamic decompensation during the hydrated, isothermic dehydrated, and time-match dehydrated conditions of protocol #2

The data are presented as mean ± 95% confidence intervals and were modeled using generalized estimating equations to account for differences in LBNP level at decompensation. Significantly different from baseline for hydrated (*), isothermic dehydrated (†), and time-match dehydrated (‡).

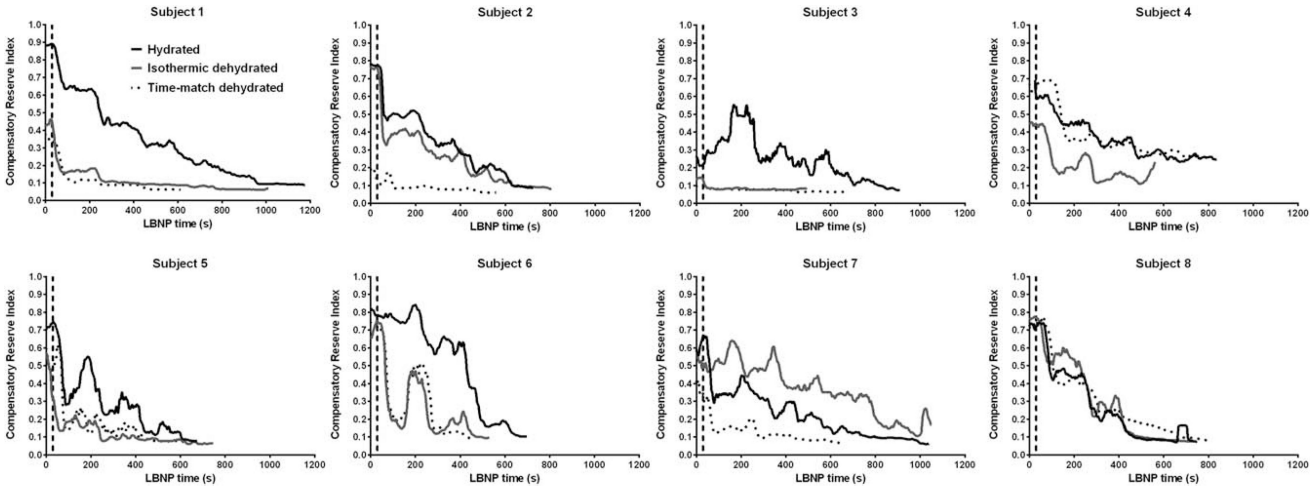

Fig. 7. Individual compensatory reserve index tracings during progressive lower body negative pressure (LBNP) to hemodynamic decompensation performed following exercise (protocol #2) during which: fluid losses were replaced (hydrated), fluid losses were not replaced and exercise lasted until the same increase in core temperature as hydrated (isothermic dehydrated), and fluid losses were not replaced and exercise lasted the same duration as hydrated (time-match dehydrated)

The dashed line indicates the start of LBNP.

Table 1

Hemodynamics and body temperatures during simulated hemorrhage performed to hemodynamic decompensation following whole-body passive heat stress or a normothermic time-control period (protocol #1)

	Baseline		Pre-LBNP		Decompensation	
	NT	**HT**	**NT**	**HT**	**NT**	**HT**
USG	1.009 (0.007)	1.012 (0.008)	–		–	
Heart rate (beats/min)	57 (8)	59 (7)	60 (10)	101 (16)*	101 (31)	130 (32)*
MAP (mm Hg)	82 (9)	82 (7)	88 (8)	77 (6)*	54 (12)	50 (10)
Tcore (°C)	37.0 (0.2)	36.9 (0.2)	37.1 (0.3)	38.2 (0.2)*	37.3 (0.2)	38.5 (0.2)*
Mean Tsk (°C)	34.0 (0.5)	34.1 (0.4)	34.3 (0.4)	39.0 (1.0)*	34.3 (0.3)	38.8 (1.3)*

Values are mean (standard deviation).

*Significantly different from normothermic ($P \leq 0.05$).

HT indicates hyperthermic; LBNP, lower body negative pressure; MAP, mean arterial pressure; Mean Tsk, mean skin temperature; NT, normothermic; Tcore, core temperature; USG, urine specific gravity.

Table 2

Measured variables during simulated hemorrhage performed to hemodynamic decompensation following dynamic exercise with and without fluid replacement (protocol #2)

	Baseline			End-exercise			Pre-LBNP			Decompensation		
	Hydrated	**Isothermic**	**Time-match**	**Hydrated**	**Isothermic**	**Time-match**	**Hydrated**	**Isothermic**	**Time-match**	**Hydrated**	**Isothermic**	**Time-match**
USG	1.011 (0.006)	1.013 (0.011)	1.011 (0.006)		—			—			—	
Heart rate (beats/min)	88 (15)	84 (14)	89 (11)	125 (14)	134 (13)	143 (21)	85 (11)	92 (11)	96 (14)	107 (27)	115 (24)	121 (26)
MAP (mm Hg)	86 (5)	83 (5)	86 (2)	86 (9)	85 (7)	87 (5)	74 (8)	78 (7)	77 (5)	42 (15)	47 (9)	42 (7)
Tcore (°C)	37.0 (0.2)	37.0 (0.2)	36.9 (0.2)	38.2 (0.1)	38.2 (0.3)	38.6 (0.5) *,†	38.1 (0.4)	38.0 (0.2)	38.5 (0.5) *,†	38.0 (0.3)	38.2 (0.2)	38.5 (0.4) *,†
Mean Tsk (°C)	35.4 (0.4)	35.4 (0.7)	35.7 (0.6)	34.5 (0.8)	35.0 (0.6)	34.7 (0.8)	35.9 (0.5)	36.6 (0.4)	36.5 (0.4)	35.7 (0.5)	36.3 (0.4)	36.0 (0.5)
Plasma osmolality (mosm/kg)	289 (7)	288 (2)	288 (2)		—		285 (3)	294 (2) *	295 (3) *	288 (3)	294 (4) *	295 (4) *
Δ Plasma volume (%)		—			—		−7.2 (2.4)	−7.6 (3.8)	−11.4 (2.4)	−12.2 (4.2)	−12.8 (5.0)	−16.1 (3.0)
Δ Mass (kg)	—	—	—	−0.1 (0.2)	−0.9 (0.5) *	−1.8 (0.6) *,†	—	—	—	—	—	—
Ex. time (min)	—	—	—	90 (0)	55 (20) *,‡	90 (0)	—	—	—	—	—	—

Values are mean (standard deviation).

* Significantly different from Hydrated ($P \leq 0.05$).

† Significantly different from Isothermic ($P \leq 0.05$).

‡ Significantly different from Time-match ($P \leq 0.05$).

ΔMass indicates change in body mass from pre to end-exercise; Ex. time, exercise time; Hydrated, exercise with fluid replacement; Isothermic, exercise without fluid replacement performed until the same increase in core temperature as Hydrated; LBNP, lower body negative pressure; MAP, mean arterial pressure; Mean Tsk, mean skin temperature; Tcore, core temperature; Time-match, exercise without fluid replacement performed for the same duration as Hydrated; USG, urine specific gravity.